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Review

Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex

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Abstract

Emotions are multifaceted, but a key aspect of emotion involves the assessment of the value of environmental stimuli. This article reviews the many psychological representations, including representations of stimulus value, which are formed in the brain during Pavlovian and instrumental conditioning tasks. These representations may be related directly to the functions of cortical and subcortical neural structures. The basolateral amygdala (BLA) appears to be required for a Pavlovian conditioned stimulus (CS) to gain access to the current value of the specific unconditioned stimulus (US) that it predicts, while the central nucleus of the amygdala acts as a controller of brainstem arousal and response systems, and subserves some forms of stimulus–response Pavlovian conditioning. The nucleus accumbens, which appears not to be required for knowledge of the contingency between instrumental actions and their outcomes, nevertheless influences instrumental behaviour strongly by allowing Pavlovian CSs to affect the level of instrumental responding (Pavlovian–instrumental transfer), and is required for the normal ability of animals to choose rewards that are delayed. The prelimbic cortex is required for the detection of instrumental action–outcome contingencies, while insular cortex may allow rats to retrieve the values of specific foods via their sensory properties. The orbitofrontal cortex, like the BLA, may represent aspects of reinforcer value that govern instrumental choice behaviour. Finally, the anterior cingulate cortex, implicated in human disorders of emotion and attention, may have multiple roles in responding to the emotional significance of stimuli and to errors in performance, preventing responding to inappropriate stimuli.

Keywords: Learning theory; Pavlovian conditioning; Instrumental conditioning; Reinforcement; Basolateral amygdala; Central amygdala; Nucleus accumbens core; Nucleus accumbens shell; Prelimbic cortex; Insular cortex; Orbitofrontal cortex; Anterior cingulate cortex; Rat; Primate; Human

Contents

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1. Introduction

Emotions are difficult to define, as the word ‘emotion’ has been applied to a diverse array of perceptions, psychological states and behavioural responses. Human emotions are particularly difficult to consider in the absence of the conscious interpretations that direct and crystallize our feelings and interpretations of emotional experiences. However, it is likely that emotions evolved from simple mechanisms that gave animals the capacity to avoid harm and seek physiologically valuable resources. Consequently, simple and evolutionarily old brain systems may serve fundamental aspects of ‘emotional’ processing, and provide information and motivation for phylogenetically more recent systems to control complex behaviour. In this sense, understanding emotional processing in animals such as rodents and non-human primates can offer insight into the neurobiology of human emotion.

The range of behaviour that has been suggested to reflect emotional states in experimental animals is large. In part, this reflects the difficulty in defining human emotions; for example, while fear has been held to be more specifically directed at a stimulus than anxiety, both have similar symptoms [1,2]. Therefore, when attempting to analyse emotional behaviour in experimental animals, many neurobiologists have chosen the pragmatic approach of studying a small number of well-defined, learned responses [3]. For example, once a rat has experienced pairings of a simple visual or auditory stimulus with electric shock, it will respond to that stimulus with immobility (freezing). The freezing response has been widely studied as an index of a central fear state [4–7], and its neural substrate is relatively well understood [3,8–10].

In contrast, learning theorists have for many decades addressed emotional learning in a broader sense, asking what information is learned during each task and subsequently represented in the brain, how these representations are formed, and to what uses they are put. Consequently, it is useful to consider under the umbrella of emotion those neural processes by which an animal judges and represents the *value* of something in the world, and responds accordingly. As will be described later, there are many such processes, and they have different uses. It is becoming increasingly clear that associative learning (including the acquisition of emotional value by a stimulus, context or event) is not a simple or unitary phenomenon. Overt behaviour is determined by the interaction of many learning and memory systems, some complementary, some competitive. Therefore, an understanding of emotion and motivation requires that these systems are recognized and characterized; behavioural neuroscientists face the challenge of teasing apart the contributions of multiple systems to behaviour in order to elucidate their neural mechanisms.

It is not the intention of this review to propose a new model of conditioning or a theory of emotion. Instead, the neural representations that govern two major classes of behaviour, Pavlovian and instrumental conditioned responding, will be considered. Using this psychological framework, the contributions of the amygdala, ventral striatum, and prefrontal cortex (PFC) to emotional and

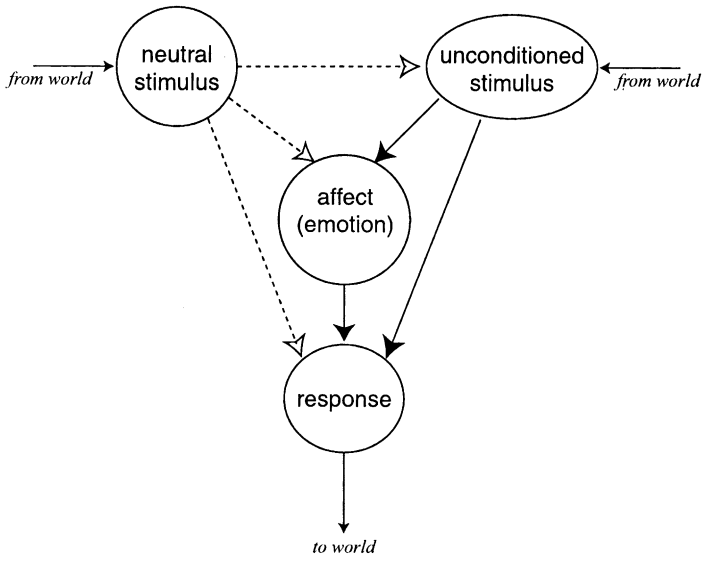

Fig. 1. Pavlovian conditioning has the potential to create associations between a conditioned stimulus (CS) and representations of the unconditioned stimulus (US), central affective or emotional states such as fear, and unconditioned responses. Only a single response is shown; distinctions between different kinds of response are discussed in the text. Dotted lines represent associative links.

motivated behaviour will be reviewed. In each case, neural systems will be related to the psychological representations to which they appear to correspond.

2. Psychological basis of emotion and motivation

Associative learning can account for the development of an emotional response. For example, the development of fear can be seen simply as a consequence of the association of an event or stimulus with an unpleasant experience. Such Pavlovian conditioning methods are regularly used to induce stimulus-specific fear in laboratory animals, dating from the time of Bekhterev [11], but are also effective in humans (first shown in Ref. [12]). Can such conditioning fully account for emotional learning? It may be that the full expression of human emotion and emotional awareness goes beyond the scope of simple conditioning. However, it is likely that much emotional behaviour is influenced by basic associative learning processes. Therefore, the associative representations that underlie Pavlovian and instrumental conditioning will be reviewed briefly before their neural bases are considered.

2.1. Pavlovian conditioning generates multiple representations of the world

The term 'Pavlovian conditioning' (or classical conditioning) refers to a set of experimental procedures, in which an experimenter arranges a contingency between stimuli in the world by presenting those stimuli independent of an animal's behaviour. The term makes no assumptions about what is learned. In a Pavlovian conditioning study, an initially neutral stimulus (such as a bell) is paired with a biologically relevant, unconditioned stimulus (US) (such as food) that normally elicits a reflexive or unconditioned response (UR), such as salivation. As a result of such pairings, the bell becomes a conditioned stimulus (CS) that is now capable of evoking salivation as a conditioned response (CR). Pavlov, the discoverer of this phenomenon [13], argued that a conditioned reflex developed because an association had formed between a representation of the CS and one of the US; this idea is termed stimulus substitution theory [13,14]. This would allow novel stimuli, through associative pairing, to control relevant innate, species-specific response mechanisms, extending the usefulness of these responses. Pavlovian conditioning allows the animal to predict events occurring in its environment, and thus adapt to different situations.

However, Pavlovian conditioning has the potential to create multiple associative representations in the brain (Fig. 1); experimental analysis has shown that CS–US pairings may cause the CS to enter into several such associations [15–17]. Thus, Pavlovian conditioning is *not* a unitary process, as acknowledged by modern theories of conditioning [18]. These representations are summarized next.

Firstly, and most simply, the CS may become directly associated with the UR, a simple stimulus–response (S–R) association that carries no information about the identity of the US [19]. However, a single US may elicit several responses; for example, a US such as a puff of air delivered to the eye may elicit a simple motor act such as blinking, and a 'central' process such as an enhancement of arousal or attention. Such US-elicited responses are sometimes considered to fall into two classes: 'preparatory' responses, which are not specific to the type of US involved (e.g. orienting to a stimulus, or enhancement of arousal), and 'consummatory' responses, which are specific to the US (e.g. salivation to food, or blinking to an air puff). As a US may elicit both a

preparatory and a consummatory response, the CS may enter into simple S–R associations with several kinds of response. In this situation, the nature of the CS itself can determine which response is evoked; for example, if a poorly localized CS such as a tone is paired with food, it may not elicit a conditioned approach response, while a localized light stimulus does.

Secondly, the CS can evoke a representation of *affect*, such as fear or the expectation of reward. This embodies the concept of an emotional 'tone' that is tagged to a stimulus. It is demonstrated by the phenomenon of transreinforcer blocking. Blocking [20,21] is a feature of Pavlovian conditioning in which an animal does not learn about one CS in the presence of another CS that already predicts the same US. In *transreinforcer* blocking, the presence of a CS previously paired with shock can block or prevent conditioning to a CS paired with the absence of otherwise expected food reward [22]. These two reinforcers share no common properties other than their aversiveness and therefore the blocking effect must depend upon an association between the CS and affect. Affective states can therefore be independent of the specific reinforcer and response—they are pure 'value' states. This concept has been widely used in theories of learning [22–24].

Thirdly, the CS can become associated with the *specific sensory properties* of the US including its visual appearance, sound, feel, and smell, but also consummatory qualities such as its taste and nutritive value. A rigorous demonstration of this kind of representation is sensory preconditioning [25], in which two neutral stimuli are first associated; one stimulus is then paired with a biologically significant US, and the other stimulus can subsequently evoke a CR. Further evidence for US specificity of Pavlovian associations comes from the effect of post-conditioning changes in the value of the US. If a CS is paired with a desirable food, and the food is subsequently devalued (by pairing it with LiCl injection to induce nausea), not only does the animal reject the food US, but its reaction to the CS changes [15,26]. Therefore, the CS could not have been associated just with an abstract affective representation, as it was able to retrieve, by association, the new value of the US. As the LiCl–food pairing does not affect the reaction to a second CS predicting a different food, each CS must have been associated with some *specific* aspect of its US.

The representations formed during Pavlovian conditioning have direct application to emotions as they are usually conceptualized. Emotions have *two* important consequences, sensory and motor. An animal that receives tone–shock pairings will show a range of autonomic and skeletal responses to the tone, but the tone will also elicit a central fear representation that may itself enter into associations and influence choice. As discussed later, lesion studies have demonstrated that these two aspects of fear are doubly dissociable. More detailed considerations of Pavlovian representations are given elsewhere [15–17,27].

2.2. Instrumental responding is controlled by multiple mechanisms

Multiple representations are not only found following Pavlovian conditioning. In an instrumental conditioning study, the experimenter arranges a contingency between the animal's behaviour and a reinforcing outcome [28]. Once again, the term refers to the experimental procedure rather than the underlying learning process. It is apparent that at least six psychological processes contribute to learning and performance of instrumental behaviour (summarized here but reviewed thoroughly in Refs. [29,30]).

Early theorists took the position that the delivery of reward strengthened an associative connection between environmental stimuli and a particular response [28,31–33]. Such learning would represent mechanistic or *procedural* knowledge [17], as the structure of the representation directly reflects the use to which the knowledge will be put in controlling the animal's behaviour, and would be inflexible, in that subsequent changes in the value of the reward would be unable to affect responding. S–R learning, which has been observed even in the spinal cord [34–36], is the archetype of 'implicit' or 'habit' learning.

While S–R learning can generate useful behaviour, it lacks flexibility; there is little room for motivational control of the performance of the response, nor is there explicit knowledge of the reinforcer. For example, if an animal is performing a habitual response that gains it food, and the value of the food changes (e.g. following food poisoning), the behaviour will persist regardless [37]. However, habits are not the only way that animals can perform actions. It is clear that many human acts are directed at particular goals and are influenced by motivational states. We can conceptualize goals and actions symbolically and such representations can be in the form of declarative or semantic knowledge. Indeed, it has been shown that rats form sophisticated and flexible representations in instrumental conditioning tasks. Behaviour may be said to be *goal-directed* if it fulfils two criteria: that it depends on the twin representations of (1) the instrumental contingency between an action and a particular outcome (A–O contingency), and (2) a representation of the outcome as a goal [30,38]. Simply put, a goal-directed organism presses a lever for food because it knows that lever-pressing produces food and that it wants the food. As performance of such behaviour requires these two representations to interact, the knowledge upon which performance is based must be *declarative*– that is, the knowledge is to some degree independent of the use to which it is put.

2.2.1. Instrumental (action–outcome) contingency

Rats can learn the instrumental contingency between lever-pressing and its consequences [39]; for example, they can be arbitrarily trained to press a lever down or to pull it up in order to obtain a goal (termed a *bidirectional control* assay). Thus, lever-pressing rats fulfil the first

Box 1
Instrumental incentive value can be dissociated from hedonic value

Stage	Control group	Comparison	Devalued group	Change occurring in devalued group
Training	L → food		L → food	
Devaluation	Food		Food → LiCl	Hedonic change
Test 1	L	=	L	
Re-exposure	Food		Food	Incentive learning
Test 2	L	>	L	

(L = lever, LiCl = lithium chloride)

During Test 1, conducted in extinction, rats from both groups respond equally on the lever. Although the food is devalued following LiCl pairing (and devalued subjects would *consume* it less than controls), the altered hedonic value of this food only comes to affect the incentive value governing instrumental responding once the animals have been re-exposed to the devalued food. Only after re-exposure do rats in the devalued group *respond* less for the food than control animals. (Based on Balleine and Dickinson [46]).

criterion for goal-directed action [29,30]. Not all behaviour may be conditioned instrumentally, however; for example, it is extremely hard to train a rodent to scratch itself for reward [40,41]. Similarly, locomotor approach, though easy to condition, may not be goal-directed. The question of whether locomotor behaviour is under the control of an instrumental A–O contingency has not been investigated directly in rats, but it has been tested in chicks. Hershberger [42] reversed the normal relationship between approach behaviour and reward using a 'looking-glass' runway, in which chicks had to run *away* from food to obtain it. A 'goal-directed' animal should be able to learn the new response–outcome contingency, but the chicks were unable to, suggesting that the approach response was directly elicited (in Pavlovian fashion) by the sight of the food bowl. Similarly, Bussey et al. [43] demonstrated that locomotor approach to a visual stimulus in rats is predominantly under the control of Pavlovian and not instrumental mechanisms, in this case by showing that the rats could not learn to withhold an approach response to a visual CS in order to be rewarded.

2.2.2. Incentive value

Rats also fulfil the second criterion: they are aware that they want the outcomes for which they work. The goal status (or *incentive value*) of an instrumental outcome can be demonstrated by devaluing it [30]. For example, if rats are trained to lever-press for food, and then receive pairings of that food with LiCl (inducing a conditioned taste aversion), they will subsequently work less for that food when tested—even if the test is conducted in extinction, when there is no opportunity to learn a new relationship between the response and the less pleasant outcome [44,45].

Surprisingly, under certain circumstances the goal status of the food does not alter *immediately*. For example, if the food is devalued by isotonic LiCl injection following a meal, rats do not work less for the food until they have had the opportunity to *re-experience* the food by consuming it [46]. This implies that there are two representations of the food's value (Box 1). After the rat has consumed food and been given LiCl, one neural representation of the food's value has been altered, such that the rat will subsequently reject that food. Garcia [47] has suggested that this representation is the affective or *hedonic* value of the food. However, the incentive value governing instrumental performance is unaffected; for a while, the two representations of value are dissociated. When the rat re-experiences the food and its new hedonic impact, the instrumental incentive value is updated, a process that Dickinson and colleagues refer to as *incentive learning* [30,46]. A similar learning process must occur before incentive values are controlled by the animal's motivational state (hunger, satiety, etc.). Thus, when a hungry rat is trained to respond for food, and then sated before being tested in extinction, it will respond as much as a hungry rat, until it experiences directly the reduced value of the food when sated [48]. After this experience, the incentive value will vary appropriately with the motivational state of the animal (implying that both the 'hedonic' system and the incentive value system have access to motivational state information).

2.2.3. Hedonic assessment

The system that reacts immediately (but covertly) to food devaluation procedures, is independent of the instrumental incentive value, and comes into play upon direct experience of the food, has been termed an affective or hedonic system [47]. To summarize this hypothesis—the devaluation procedure modifies the neural system responsible for hedonic experience, so that it will react with disgust rather than pleasure when the devalued foodstuff is next experienced. In the meantime, the more 'cognitive' incentive value remains high, so the animal still works for the devalued food. The next time the food is consumed, direct experience of the food leads to the disgust reaction being evoked, which rewrites the neural representation of incentive value and leads the animal to work less for the food in the future.

Although hedonic reactions may be conditioned and assessed in humans by direct questioning [49], it is not obvious that they can be assessed at all in other species. However, it has been suggested that taste reactivity patterns—the orofacial reactions of rodents to flavours introduced into the mouth—are an index of hedonic

experience in rats [50], and indeed, they behave in a manner compatible with the role required by Dickinson and colleagues of their hedonic system, such as tracking motivational state directly [51–54].

2.2.4. Discriminative stimuli

When responding is rewarded in the presence of a stimulus but not in its absence, that stimulus is established as a discriminative stimulus (S^D). Although the S^D may also serve as a Pavlovian CS [55], S^Ds have effects that cannot be explained in this manner [56]: there is a conditional relationship in which an S^D signals the operation of a particular response–reinforcer (instrumental) contingency [57–59].

2.2.5. Stimulus–response habits

Although rats possess declarative knowledge of the consequences of their actions, this does not mean that they lack a procedural S–R 'habit' system. There have been a number of demonstrations in which reinforcer devaluation failed to affect instrumental responding (reviewed in Ref. [37]). Adams [37] established that overtraining is one critical determinant of whether an instrumental response becomes 'autonomous' and resistant to devaluation. Following limited experience of instrumental training, rats' actions remained under the control of the instrumental contingency, and were responsive to reinforcer devaluation. With extended experience of instrumental responding, their actions became habitual, inflexible, and resistant to devaluation [29,60–62].

2.2.6. Pavlovian–instrumental transfer

Finally, Pavlovian CSs can modulate instrumental performance [29,30], an effect termed Pavlovian–instrumental transfer (PIT). For example, a stimulus that predicts the arrival of sucrose solution will enhance lever-pressing for sucrose; this is the basic phenomenon of PIT [63,64]. This appears to occur by two mechanisms [29,30]. Firstly, these stimuli may have a *general* motivating effect: when a CS predicts an outcome that is desirable in the animal's current motivational state, instrumental responding is enhanced, even if the rat is working for a different outcome [65]. This has been termed *conditioned motivation* [66]. For example, a CS for a sucrose solution will enhance lever-pressing for sucrose—but also for dry food pellets—when the animal is thirsty [67]. CSs may also act selectively to potentiate actions with which they share an outcome (in this example, potentiating lever-pressing for sucrose more than for food); this is a *response-* or *outcome-specific* form of PIT [55].

As the ability of a Pavlovian CS to affect instrumental performance depends upon the relevance of the US to the animal's motivational state, a neural system must exist to judge the value (or salience) of the US when the CS is presented. Indeed, the 'Pavlovian value' depends *directly* on motivational state in a way that instrumental incentive value does not [67–69], implying that it is a separate valuation process. Indeed, these two processes have been dissociated pharmacologically [70]. Similarly, as Pavlovian processes can affect responding without altering instrumental incentive value [69], it seems probable that they are also separate from hedonic value. It is presently unclear whether a CS can also elicit a motivational response in a direct, 'habitual' way (that is, without going through a representation of the US). However, investigations of the basis of PIT are important as this process probably plays a major role in CS-precipitated reinstatement of instrumental responding, exemplified by cue-induced relapse in drug addiction [71–73].

2.2.7. Summary

The complex interaction of processes governing instrumental responding is summarized in Fig. 2. It is clear that an ostensibly simple behaviour—lever-pressing in rats—is influenced by many dissociable psychological processes. Understanding of these processes has deepened in recent decades, but outstanding questions remain. Prominently, there is a clear equivalence between some of the associative representations inferred to exist from instrumental and from Pavlovian studies—for example, aspects of PIT require a CS–US representation that encodes sensory aspects of the US and is formed by Pavlovian conditioning. However, it is at present uncertain as to how central states of 'affect' (described earlier) are related to the 'values' governing instrumental action. Furthermore, there are processes which clearly involve emotional or motivational learning but for which the precise psychological basis is unclear. An example is conditioned reinforcement (CRf), in which neutral stimuli paired with primary reward gain affective or motivational value such that animals will work for them [27,74–76]. Such stimuli might act in multiple ways (perhaps gaining instrumental incentive value but also affecting behaviour via PIT); thus, it is not presently clear how CRf relates to the valuation processes discussed earlier.

2.3. The neural basis of conditioning

Characterizing the psychological processes contributing to behaviour is important, as it is highly likely that theoretically distinct processes have dissociable neural bases. Thus, our understanding of the neural mechanisms underlying emotion and motivation is likely to progress most rapidly once the psychological mechanisms influencing behaviour are recognized. In the next three sections, we will review the contributions of the amygdala, nucleus accumbens, and PFC to emotion and motivated behaviour, using the learning-theory framework outlined earlier.

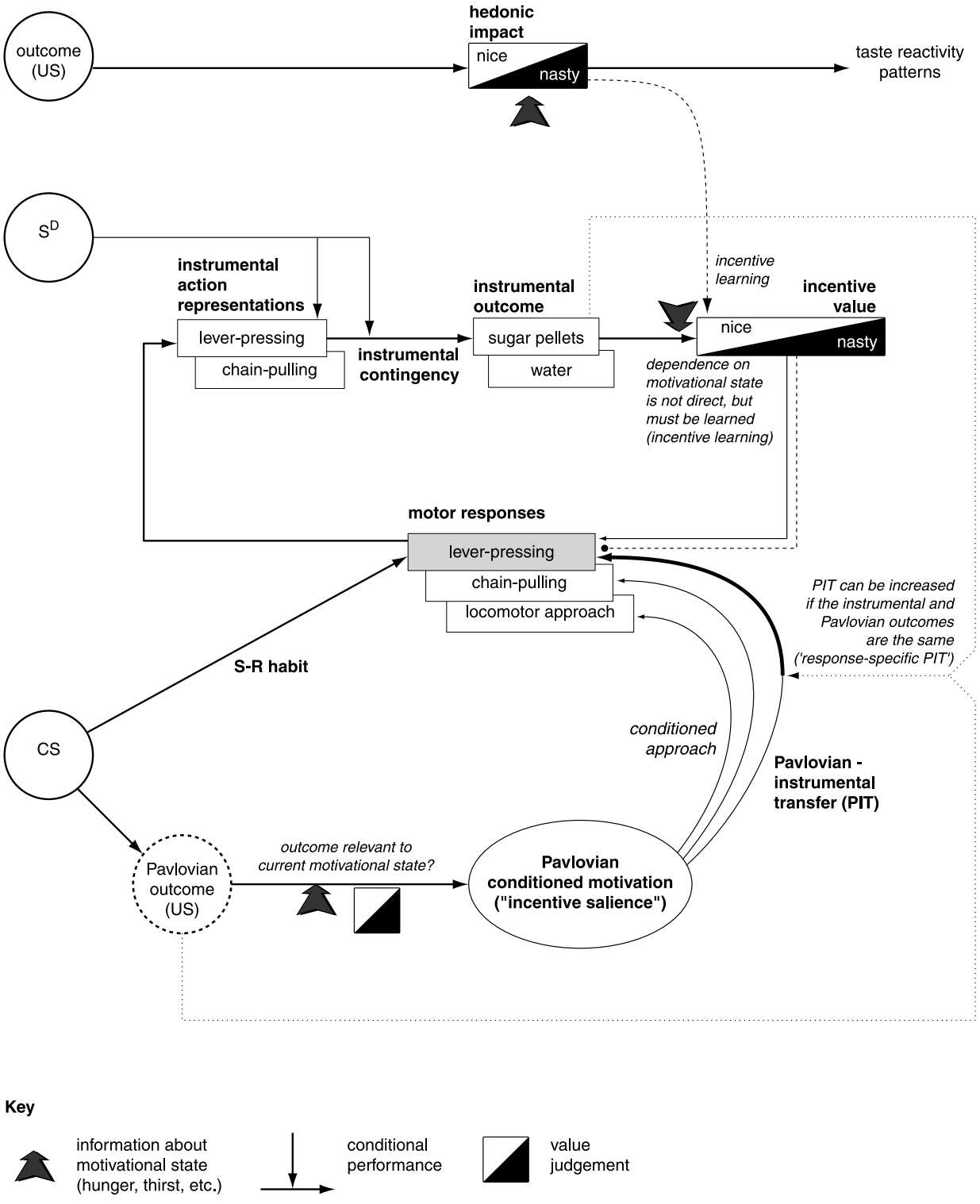

Fig. 2. Some processes that contribute to instrumental behaviour in rats. An action such as lever-pressing is capable of being detected and represented in a system that can encode the contingency between this action and outcomes. When this representation is combined with a favourable representation of the instrumental incentive value of the outcome, lever-pressing is promoted. The instrumental contingencies currently in force can be signalled by instrumental discriminative stimuli (S^Ds). The value governing goal-directed responding is learned through direct experience of the outcome in particular motivational states; it can therefore be distinguished from a hedonic, or immediate-assessment value system (see text). A separate contribution to response output comes from direct stimulus–response associations (S–R habits), which can be formed through repeated training. In addition to these processes, Pavlovian conditioned stimuli (CSs) that signal a motivationally relevant outcome can enhance responding (Pavlovian–instrumental transfer), both by providing a 'motivational boost' and by potentiating responses that share an outcome with the Pavlovian CS. Finally, not all kinds of response can be represented instrumentally; for example, conditioned locomotor approach is under the control of predominantly Pavlovian mechanisms.

3. Contributions of the amygdala to emotion and motivation

3.1. The amygdala consists of a group of nuclei involved in emotional learning and expression

The amygdala is probably the structure most implicated in emotional processing. Since the demonstration that monkeys with amygdala lesions were 'fearless'—part of the Klüver–Bucy syndrome [77]—it has been recognized that the amygdala is a key element of the neural basis of emotion. Damage to the amygdala in humans may lead to an increase in threshold of emotional perception and expression [78–80]; amygdala lesions certainly cause impairments in emotional learning [81], deficits in the perception of emotions in facial expressions [82,83], and impaired memory for emotional events [84].

Neuroanatomically, the amygdala comprises several subnuclei which have been grouped into cytoarchitectonic and functional units by many authors [85–90]. Two such units that have been particularly implicated in the control of emotional processes are the central nucleus (CeA) and the basolateral amygdala (BLA). The BLA comprises the lateral, basal and accessory basal nuclei, which have a peri-isocortical neuronal structure [88,90,91]. While the BLA and CeA are both evolutionarily old [92], the BLA has undergone comparatively recent expansion [93]. The BLA has extensive reciprocal projections with polysensory neocortex and the frontal lobes, and projects heavily to the ventral striatum and the CeA (Fig. 3). The CeA has a distinctive striatal morphology and connectivity and may subserve a phylogenetically simpler function than the BLA. A prevailing view is that the BLA is responsible for emotional Pavlovian learning; receiving sensory information via the lateral amygdala, it acts as a site of CS–US association and uses this learned information to control the activity of the CeA. In turn, the CeA acts as a 'controller of the brainstem', using its widespread projections to the hypothalamus, midbrain reticular formation and brainstem to orchestrate behavioural, autonomic, and neuroendocrine responses. The amygdala does indeed operate in this way in some situations [1,3,9,10,94–98]. However, the BLA does more than control the CeA: it projects to structures including the ventral striatum and PFC, enabling it to influence complex behaviour [99–101]. Additionally, the CeA itself receives direct sensory input [85,90,102,103] and may be capable of learning and/or subserving behavioural expression, independently of the BLA [99,104–107]. What types of learning, then, depend upon these amygdaloid nuclei, and what representations do they subserve?

3.2. Amygdaloid subnuclei operate in series, but also in parallel

The amygdala is clearly involved in Pavlovian conditioning of 'emotional' responses. Two measures frequently taken to indicate emotional states of fear in rats are freezing, a species-specific response to danger in which a rat remains motionless, and fear-potentiated startle, in which the presence of a stimulus signalling danger enhances the startle reflex to a loud noise. Lesions of either the BLA or CeA impair aversive conditioning indexed by measures of freezing and fear-potentiated startle [9,10]. LeDoux [3] suggests that the sensory thalamus, sensory neocortex, and hippocampus convey increasingly complex information about environmental stimuli (CSs) to the BLA, where CS–US association takes place. Furthermore, lesions of these structures, and lesions of targets of the CeA, such as the periaqueductal grey (PAG), lead to impairments in conditioned freezing [1,3,9,10]. A parsimonious hypothesis incorporating these data is that the BLA acts as the associative site for stimulus–outcome representations and the CeA provides the output pathway through which these associations gain access to appropriate responses, such as the conditioned freezing response. This is a *serial* model of BLA/CeA function. Indeed, stronger forms of this hypothesis have been advocated: that fear conditioning does not survive without the basolateral amygdaloid complex and that the CeA is not capable of supporting associative function without the BLA [108].

However, not only can some forms of fear conditioning occur in animals in which the BLA has been lesioned, but the involvement of the BLA and CeA in aversive and appetitive associative learning can be dissociated. Selden et al. [109] demonstrated that certain forms of fear conditioning may survive BLA lesions—specifically, contextual fear conditioning (as assessed by an aversion to the environment in which the subjects experienced shock). A *double* dissociation of the effects of BLA and CeA lesions was shown more recently by Killcross et al. [104]. When rats were trained to respond on two levers for food, one of which intermittently produced a CS followed by mild electric shock, they exhibited two phenomena: instrumental avoidance (voluntarily biasing their responding away from the lever producing the CS and shock) and Pavlovian conditioned suppression (inhibition of lever-pressing during presentation of the CS). Whilst BLA lesions impaired instrumental avoidance, they did not affect conditioned suppression. In contrast, lesions of the CeA produced the opposite effect—preserved active avoidance and persistently impaired conditioned suppression. An analogous double dissociation using an appetitive version of the task was recently reported [110]. Similarly, Hitchcott and Phillips [106] have demonstrated a double dissociation of the effects of the dopamine (DA) D2/D3 receptor agonist 7-OH-DPAT injected into the CeA and BLA, affecting Pavlovian conditioned approach and instrumental responding for an appetitive conditioned reinforcer, respectively. Hatfield et al. [107] have demonstrated a double dissociation even within the domain of appetitive Pavlovian conditioning, between second-order conditioning (requiring the BLA but not the CeA) and conditioned orienting (requiring the CeA but not the BLA), discussed later.

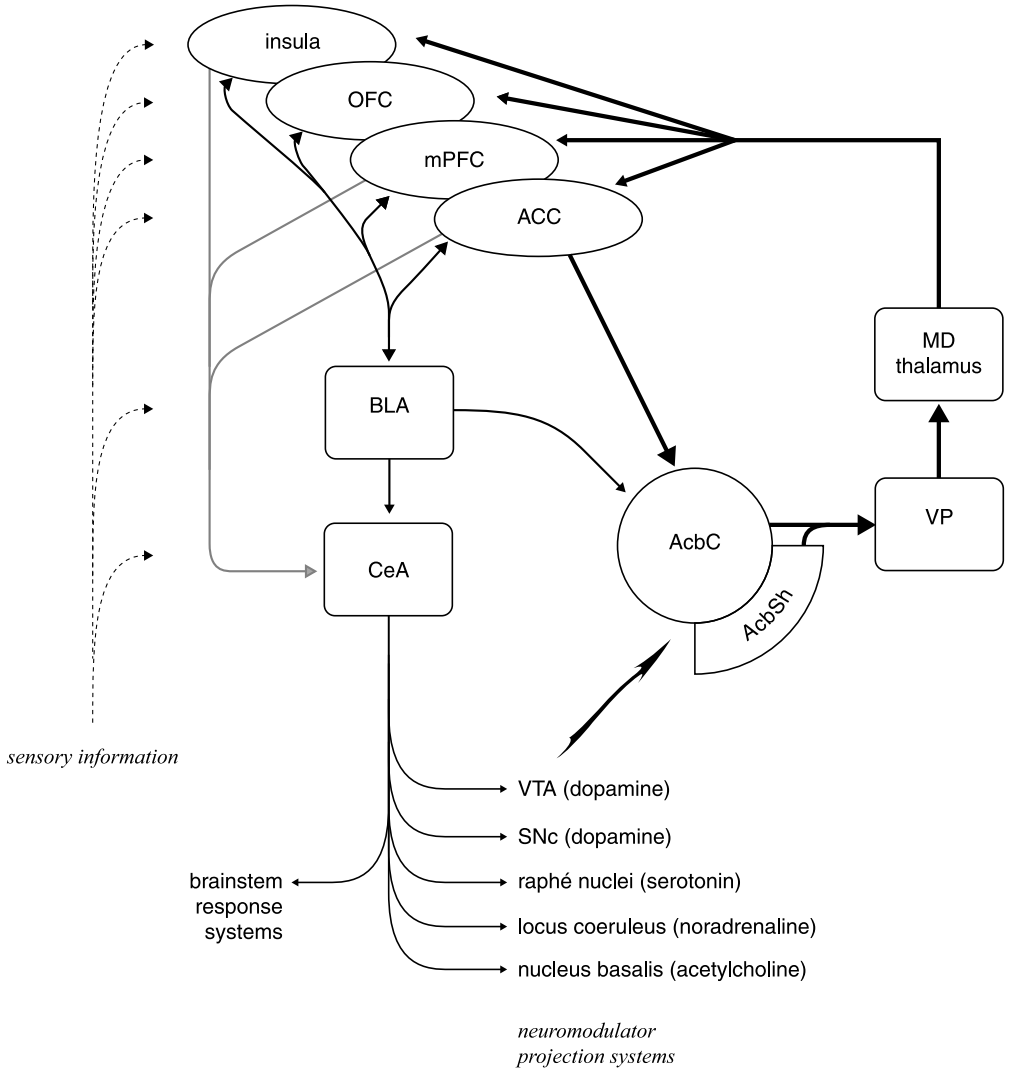

Fig. 3. Simplified schematic illustrating components of the limbic corticostriatal loop (heavy lines) and the relationships between regions of the prefrontal cortex, amygdala, and ventral striatum discussed in the text. For clarity, hippocampal structures are not shown. (Abbreviations: OFC, orbitofrontal cortex; mPFC, medial prefrontal cortex; ACC, anterior cingulate cortex; BLA, basolateral amygdala; CeA, central nucleus of the amygdala; VTA, ventral tegmental area; SNc, substantia nigra pars compacta; AcbC, nucleus accumbens core; AcbSh, nucleus accumbens shell; VP, ventral pallidum; MD, mediodorsal.) *Prefrontal cortex*. Several prefrontal cortical regions contribute to instrumental behaviour. The insular cortex, containing the primary gustatory neocortex, is required for the memory of specific sensory properties of foods; this information is used to retrieve the instrumental incentive value of a foodstuff. The neural representation of incentive value itself is not well understood, but both the OFC and the BLA (which interact with each other) are candidate regions that influence choice behaviour by providing information about the value of stimuli and reinforcers. The mPFC is required for the detection of instrumental A–O contingencies, and thus conveys information about how to obtain valued goals. The ACC's functions are complex, as discussed in the text, but one of those functions may be to correct errors in ongoing responses, in situations where several environmental stimuli predict outcomes of different value, thus preventing responding to unrewarded stimuli. *Amygdala*. In the domain of Pavlovian conditioning, the BLA uses incoming sensory information about a CS to retrieve the current emotional or motivational value of the predicted US. It can use this value information to influence instrumental choice behaviour, but can also control simple conditioned responses through the CeA. The CeA, which controls a variety of brainstem response systems including autonomic control centres, can additionally influence arousal and attentional processes through its projections to the chemically defined systems of the reticular formation; for example, influencing cortical learning through its control of the cholinergic nucleus basalis. The CeA can also learn simple stimulus–response associations independently of the BLA, and probably plays an important role in regulating the dopaminergic innervation of the limbic corticostriatal loop. *Ventral striatum*. Finally, the nucleus accumbens provides motivational drive to behaviour. The AcbSh may mediate some of the motivational impact of primary reinforcers (unconditioned stimuli), while the AcbC contributes Pavlovian conditioned motivation to ongoing behaviour (an effect magnified by the dopaminergic innervation of the nucleus accumbens), and promotes the selection of actions that lead to delayed rewards.

These data therefore support a *parallel* processing view of amygdala function, in which representations stored in (or communicated through) the CeA and BLA can affect behaviour through separate afferent and efferent pathways. As described earlier, it is notable in this regard that the CeA (as well as the BLA) receives sensory input from the thalamus [102,103] and cortex [90], which would support association formation independent of the BLA [111], and that the BLA

and CeA have dissociable and complementary efferent projections. With these data in mind, we will review studies in which the theoretical basis of the CR is clear, and use these results to discuss amygdala-dependent tasks which are less well understood psychologically.

3.3. The basolateral amygdala is required for a Pavlovian CS to gain access to the current motivational or affective value of the specific US that it predicts

It is clear that rats with BLA lesions are able to acquire CRs [104,105,107,109,110,112]. However, these responses do not have the flexibility seen in intact animals. Specifically, they are insensitive to subsequent changes in the value of the US (reinforcer revaluation). For example, rats with BLA lesions have been shown to acquire normal conditioned responding to a CS paired with food (the CR being approach to the cup into which food was delivered [107]). BLA-lesioned rats also showed normal acquisition of an aversion to that food when it was subsequently paired with LiCl [107,112,113], but failed to adjust their responding (orienting and food cup approach) to the CS spontaneously after the food was devalued [107]. Similar results have been observed in monkeys [114]. The most parsimonious explanation is that the CRs learned by the BLA-lesioned rats were a result of direct associations between the CS and the response (Pavlovian S–R associations). They lacked the ability to use the CS to access the value of a specific US and use that representation to alter their response—an ability defined by Holland [115] as 'mediated performance': the capacity to respond based on a CS-activated representation of the US.

The idea that BLA-lesioned animals cannot use a CS to gain access to the current value of its specific US has great explanatory power. In second-order conditioning, a stimulus CS_1 is paired with a US, and a second stimulus CS_2 is then paired with CS_1. A second-order CS becomes associated with the affective value that is called up by the first-order CS, rather than its sensory properties [16,27]. Similarly, CRf depends on the affective or motivational value gained or accessed by the CS. BLA-lesioned rats cannot acquire second-order conditioning [107], cannot acquire responding under second-order instrumental schedules [116,117], and cannot use a first-order CS as a conditioned reinforcer [118,119]. Thus, the responses that still occur to the first-order CS in BLA-lesioned animals do not support second-order conditioning. However, the deficit in BLA-lesioned animals is not restricted to second-order conditioning, as BLA lesions also impair reward devaluation effects following first-order conditioning, as discussed earlier [107]—another task that requires the subject to retrieve the affective value of the US using the CS. Specific modulation of instrumental choice behaviour by a CS also requires that the subject utilizes the motivational value of a particular US; this capability, too, depends upon the BLA [104,110]. These studies also demonstrate that BLA lesions affect both appetitive and aversive conditioning [99].

Conditioned freezing. Associations between a CS and the affective value of a US may account for responses such as conditioned freezing, which cannot readily be accounted for in terms of a CS–UR association. Firstly, there is reason to believe that freezing is not a UR [27]. The immediate UR to shock is not freezing, but agitation, jumping, vocalization and escape [4–7]. At the time of conditioning, therefore, there is no freezing response occurring to which a CS–UR association can be formed [120].

Secondly, after the initial locomotor response to the shock, a freezing response may subsequently be generated (so-called post-shock freezing). However, substantial evidence suggests that, rather than being a UR to the shock presentation, this is the expression of a conditioned association formed between the shock and the experimental context. Three pieces of evidence support this conclusion: (i) if animals are moved to a separate context immediately after shock presentation they show no freezing; (ii) animals receiving a shock directly after being placed in a novel context show no freezing (the so-called 'immediate shock freezing deficit' [6,7]); (iii) finally, and most convincingly, if the rat has had extensive prior experience of the context in which it is shocked, such that latent inhibition occurs to that context, post-shock freezing is not observed [121].

Thirdly, freezing is a US-specific CR (an adaptive response to environmental danger): thus, while freezing occurs to a CS for shock, it does not occur to a CS for the omission of expected food, even though both signal aversive events. It seems plausible to suggest, therefore, that the BLA is critical for the acquisition of conditioned freezing because it subserves the formation of a stimulus–outcome association between the CS and a neural representation of the affective properties of the particular US—that is, fear [122].

Fear-potentiated startle. In the phenomenon of fear-potentiated startle, an aversive CS induces a state in which a startle-inducing stimulus (such as a loud noise) causes a greater startle reflex than it would in the absence of the CS. The state retrieved by the CS is affective, i.e. fear [16]; it is thereby sensitive to BLA lesions or inactivation [123,124].

Summary. This hypothesis might be summarized by saying the BLA is necessary for a CS to retrieve the value of its specific US; once retrieved, this value may be used to control multiple responses (such as freezing, fear-potentiated startle, and instrumental choice behaviour) via different output systems.

Outstanding questions. Five major questions about BLA function remain. Firstly, with regard to emotion itself, it is not known whether BLA-lesioned animals lack affective states entirely, or are merely unable to call them up via a CS. As amygdala lesions do not affect food preferences (other than to reduce food neophobia [125,126]), the latter appears more likely—thus, the most plausible role for the BLA is in maintaining a representation of the affective or

reinforcing properties of conditioned cues through direct connections with representations of the specific values of primary reinforcers, maintained elsewhere. More specifically, it is possible (but presently uncertain) that BLA-lesioned rats can form CS–affect associations that are totally devoid of US specificity, allowing them to develop conditioned taste aversions [107,112]. Conditioned taste aversions may be unusual in that they depend on direct CS–affect associations of this sort [127], as habituation to the US (e.g. LiCl) does not alter responding to the CS in normal animals [128,129]. This is controversial [15], as is the effect of BLA lesions on conditioned taste aversions [113]. It is clear, however, that BLA-lesioned rats cannot use a CS to retrieve the current motivational value of the specific US [107]. Experimental techniques that allow 'pure affect' to be measured, such as transreinforcer blocking (described earlier) may allow this complicated question to be answered more precisely.

Secondly, it is at present unclear whether the BLA is also involved in representing specific sensory information about USs, required for stimulus–stimulus (S–S) associations [99]. According to this view, BLA-lesioned animals make URs and learn simple CS–UR associations, including 'emotional' responses, but the CS conveys no information about the identity of the US. However, each sensory modality projects to a region of sensory cortex, a reason to question a priori whether the BLA is required for S–S associations, and rats can learn stimulus discrimination tasks in the absence of the BLA [130–132]. An alternative explanation, therefore, is that the US-specific representation involving the BLA is purely affective; according to this view, BLA-lesioned animals can learn CS–UR associations that are incapable of affecting instrumental choice behaviour, and can learn CS–US(sensory) associations, but cannot learn CS–US(affective) associations, and the sensory representation they can activate is without affective valence (see also Ref. [115] for a discussion of this possible dissociation). Following a recent demonstration that BLA lesions do not impair sensory preconditioning [133], which depends instead on sensory areas such as perirhinal cortex [134], the latter interpretation seems most likely.

Thirdly, the importance of the BLA's contribution to Pavlovian conditioning may change with training; this is presently an under-investigated area. For example, it has been shown that overtraining can mitigate the deficits in conditioned freezing to contextual cues exhibited by BLA-lesioned rats [104,135–140]. It is an intriguing speculation that this might reflect changes in the psychological basis of conditioned responding that normally occur with prolonged training—perhaps that the contribution of conditioned *affect* (and hence the BLA) is most important early in training [15,141].

Fourthly, the contribution of the BLA to instrumental conditioning requires further investigation. Undoubtedly, BLA-lesioned rats are impaired at instrumental responding for a Pavlovian CS, serving as a conditioned reinforcer [118,119]. In contrast, lesions of the BLA do not impair the general form of PIT [142–144], though they may disrupt the *specificity* with which Pavlovian CSs influence instrumental responding [143]. These data are compatible with the view that BLA-lesioned rats can learn simple Pavlovian CRs but not retrieve the value of specific USs. However, it is not known whether BLA lesions disrupt core aspects of instrumental conditioning, such as A–O contingency perception and the attribution of instrumental incentive value. Although BLA-lesioned rats can acquire simple instrumental responses [130,144], it is likely that the BLA has some role in governing the incentive *value* of the goals of behaviour. Thus, while amygdala lesions do not impair preferences between foods [125,126], such lesions affect monkeys' sensitivity to changes in the values of specific foods [114], while disconnecting the amygdala from the orbitofrontal cortex (OFC) impairs the ability of rhesus monkeys to adjust their choice behaviour in response to reinforcer devaluation [145].

Finally, the BLA has a prominent role in the emotional modulation of memory storage. It is part of the mechanism by which emotionally arousing situations improve memory (reviewed thoroughly in Refs. [84,146]). For example, BLA is the critical site for the memory-enhancing effects of systemic adrenaline and glucocorticoids, and for the amnesic effects of benzodiazepines [146]. As many studies in this field have used tasks such as active avoidance and spatial memory, which may require contributions from several of the Pavlovian and instrumental representations described earlier, it will be of great interest to establish whether the BLA's role in memory consolidation can be tied to a particular type of psychological representation, such as the acquisition but not the maintenance of the value of CSs [114]—or whether this modulatory function of the BLA is independent of the information that it retrieves in Pavlovian conditioning tasks.

3.4. The central nucleus of the amygdala is a controller of brainstem arousal and response systems, and also subserves some forms of stimulus–response Pavlovian conditioning

The CeA is justly seen as a controller of the hypothalamus, midbrain and brainstem [111]. The CeA projects to a variety of autonomic and skeletomotor control centres involved in aversive conditioned responding [1], including the periaqueductal grey (PAG) (which mediates the freezing response), the lateral hypothalamus (which mediates sympathetic activation), and the caudal pontine reticular nucleus (PnC, which mediates potentiation of the startle reflex). The CeA also projects to reticular formation nuclei that provide the chemically-defined, diffuse projection systems to the forebrain, such as the dopaminergic ventral tegmental area (VTA) and substantia nigra pars compacta (SNc), the noradrenergic locus coeruleus, the serotonergic raphé nuclei, and basal forebrain cholinergic nuclei. As might be expected, a number of CRs are dependent upon

the CeA and its projection to this array of nuclei [99]. In seeking a description of the CeA's function, it is useful to consider the similarities and differences between the effects on behaviour of manipulating this nucleus and the BLA.

A number of Pavlovian conditioning tasks require the BLA but not the CeA. Thus, while producing deficits in a number of tests of Pavlovian conditioning, lesions of CeA (unlike those of the BLA) do not impair second-order conditioning [107], or responding for CRf [147]. Hatfield et al. [107] and Gallagher et al. [148] also showed that CeA-lesioned rats can acquire some first-order appetitive CRs (such as conditioned behaviours directed at a food source). Those first-order CRs that they do acquire are sensitive to reinforcer devaluation [107], implying that in CeA-lesioned rats a CS can still gain access to information about the identity and current value of its associated US.

Several specific Pavlovian CRs require the CeA, but also the BLA. While CeA lesions abolish conditioned freezing, fear-potentiated startle and conditioned bradycardia [1,95,97,98,111,149–152], these behaviours are also sensitive to BLA lesions (as discussed earlier, and see Ref. [153]) and appear to depend on the CeA simply because the BLA gains access to these motor nuclei (PAG, PnC, dorsal motor nucleus of the vagus) via the CeA—part of its role in a serial circuit [3,111]). One prediction arising from this view is that temporary inactivation of the CeA during fear conditioning should not prevent a subsequent conditioned freezing response; this experiment has not yet been performed.

Potentially the more interesting group of CeA-dependent CRs, however, are those for which the CR depends on the CeA but *not* on the BLA. One such aversively motivated CR is conditioned suppression, described earlier [104]. Although it is possible to induce cessation of licking behaviour by presenting a CS paired with strong (e.g. $\geq$0.5 mA) electric shock, such a CS will induce conditioned freezing [94,121], which is obviously incompatible with licking behaviour. As might be expected, conditioned suppression that is attributable to freezing is impaired by BLA lesions [94,109]. However, if mild (e.g. 0.2 mA) shock is used, conditioned suppression of ongoing instrumental responding is induced in the absence of freezing [104], in which case the conditioned suppression represents aversive PIT and it survives BLA lesions but is persistently impaired by CeA lesions [104].

Similarly, there are appetitive CRs that depend on the CeA but not the BLA. For example, the rat's orienting response (OR) can be conditioned to a CS for food; conditioned ORs depend on the CeA (but not the BLA) [107,148], and the critical circuit appears to involve the projection from the CeA via the DAergic SNc to the dorsolateral striatum [154]. Despite the lack of the CR, the corresponding UR remains unimpaired in CeA-lesioned rats [148].

Conditioned locomotor approach is another appetitive CR that depends on the CeA but not the BLA. We have studied an autoshaping task [155] adapted for rats [43], in which a visual stimulus (CS+) is presented on a computer screen and followed by the delivery of food in a different spatial location; a second stimulus (CS−) is also presented, but never followed by food. Though the subject's behaviour has no effect on food delivery, animals develop a CR of selectively approaching the CS predictive of food, before returning to the food hopper to retrieve the primary reward. Autoshaping has been shown to be a Pavlovian CR [27,43,156–158]. While BLA lesions do not impair autoshaping, lesions of the CeA do [105]. As acquisition of the autoshaping CR requires the AcbC [159] and its DAergic innervation [160,161], and as the CeA does not project directly to the Acb [85,162–165] but does project to the VTA [86,166–169], it may be that this CR depends on the regulation by the CeA of the DAergic projection from the VTA to the AcbC [99,100,170]. Further evidence that the CeA is important in conditioned approach has been provided by Hitchcott and Phillips [106], who found that post-training intra-CeA injection of a dopamine (DA) receptor agonist enhanced conditioned approach behaviour, while intra-BLA injections did not.

The role of the CeA also extends to Pavlovian conditioned motivational influences on instrumental action. Thus, PIT is abolished by lesions of the CeA, but not the BLA [104,110,144]; similarly, lesions of the CeA (but not the BLA) impair the ability of dopaminergic agonists to enhance responding for CRf [118,147]. We discuss this later when we consider functions of the ventral striatum, and suggest that these effects also indicate that the CeA influences the VTA to provide a conditioned motivational influence on behaviour.

Additionally, Gallagher, Holland and co-workers have shown that the CeA is involved in the control of attentional aspects of stimulus processing, through its projections to the reticular formation. The CeA plays a role in visuospatial attention during continuous-performance tasks [171], and also appears to regulate the *associability* of stimuli under certain circumstances [172–174]. Associability is a learning-theory concept [175,176]; it determines how much processing is devoted to a CS, and therefore indirectly determines the degree to which new things can be learned about the CS. The Pearce and Hall [175] model of Pavlovian conditioning suggests that when a CS is reliably followed by a US, the CS may be worth responding to, but is not worth learning about: animals should confine their attention to learning about stimuli whose consequences are less well known. Associability can be increased by surprising events: for example, if a light is regularly followed by a tone, presentation of the light on its own (with the surprising absence of the tone) is predicted by the Pearce–Hall model to increase the subsequent associability of the light [177,178]. This phenomenon—specifically, the ability to *upregulate* associability—appears to depend upon the integrity of the CeA [179,180], together with its projections to cholinergic neurons in the nucleus basalis magnocellularis (NBM) [181], and possibly from there to the posterior parietal cortex [178]. Though the cellular basis

of associability is unknown, it is interesting to note that Weinberger and colleagues have shown that auditory cortex receptive fields for a CS of a particular frequency expand, at the expense of other regions, when that CS is paired with an aversive US. This cortical plasticity depends upon muscarinic acetylcholine (ACh) receptors and can be induced by stimulation of the NBM [182–184], just as ACh-dependent cortical EEG activity can be induced by CeA stimulation [111]. Expansion of a sensory receptive field might be one mechanism by which the associability of a stimulus could increase, as might increased attention to that stimulus directed by the attentional circuits known to exist in the posterior parietal cortex [185].

How can these functions of the CeA be brought together conceptually? Even though it receives neuronal afferents appropriate to support them, there is no direct evidence to suggest that the CeA is itself a site of association; it might receive an already-associated input. However, it is clear that animals lacking a BLA can form some kinds of association, the conditioned expression of which is sensitive to CeA, but not BLA, lesions [104,105,142,144,172]. The simplest analysis at present seems to be that the CeA does form simple CS–UR ('sensorimotor') associations, which do not depend upon a specific US: that is, they are independent of the identity and current motivational value of the US and are also unable to support second-order conditioning. We have suggested [99] that the responses subserved by CeA-dependent associations especially include the modulation of reflexes organized within the brainstem, including some that might conventionally be regarded as 'affective', including conditioned suppression, conditioned orienting, and PIT. These are all disrupted by CeA but not BLA lesions. Responses such as conditioned suppression may influence instrumental behaviour non-specifically (i.e. influence the ongoing level of all instrumental responses), but are insufficient to modulate instrumental behaviours differentially (i.e. affect choice) [104]. Finally, just as the BLA has a role in memory modulation [146], the CeA also modulates the associability of representations stored elsewhere in the brain [172–174].

It would be elegant if the representations encoded by amygdalar nuclei could be entirely categorized using a well-defined psychological dichotomy. It appears that we are remarkably close to this situation with the suggestion that the CeA encodes or expresses Pavlovian S–R (CS–UR) associations, while the BLA encodes or retrieves the affective value of the predicted US. However, not all S–R associations depend on the CeA. For example, nictitating membrane/eyeblink conditioning depends instead on the cerebellum, even though the eyeblink clearly is part of the UR to eyeshock; this circuit has been extensively mapped [186] and appears to involve CS–UR associations. Eyeblink conditioning can occur in the absence of the amygdala (even though simultaneously conditioned changes in heart rate are amygdala-dependent). In attempting to define the purview of cerebellar conditioning, Steinmetz [187] comes to a more pragmatic, neurobiological solution: the cerebellum has been shown to be involved in associative learning when: (1) a simple motor response is involved; (2) the CS–US interval is shorter than ~4 s; (3) the US is aversive; (4) the US not only causes a UR, but in addition activates the inferior olive, the 'teaching system' for such cerebellar learning. This definition fits no neat psychological category so far proposed. Applying this rationale to the amygdala, for example, would lead to the suggestion that the CeA subserves Pavlovian CS–UR associations when that response is controlled by a hypothalamic or brainstem nucleus governed by the CeA; such responses include autonomic changes, motivational arousal and attentional enhancement.

3.5. Summary

It appears likely that the BLA stores associations which allow the CS to retrieve the affective or motivational value of its particular US, a form of Pavlovian stimulus–outcome association. This information can be used to control the CeA and thereby its hypothalamic, midbrain and brainstem targets, giving rise to 'affective' responses such as freezing or fear-potentiated startle and modulation of arousal and attention. The BLA can also use this information to modulate instrumental actions, presumably via its projections to the ventral striatum or PFC (discussed next). In addition to its role as a recipient of information from the BLA, the CeA also receives parallel input from cortical and subcortical structures; it receives or may encode direct S–R Pavlovian associations, thereby influencing specific CRs organized in the hypothalamus, midbrain, and brainstem, as well as modulating arousal and attention through the diffuse projection systems of the reticular formation.

4. The nucleus accumbens and its associated corticostriatal circuitry

Though the amygdala influences simple, innate behavioural patterns through its projections to the hypothalamus and brainstem, the motivational effects of emotionally significant stimuli are mediated in part by the ventral striatum, specifically the nucleus accumbens (Acb) [170]. While the Acb conforms broadly to the pattern of the cortico-striatal-pallido-thalamo-cortical 'loop' typical of the striatum [188,189], it is a recipient of information from a considerable array of limbic structures (including the amygdala, hippocampal formation, and regions of the PFC; see Fig. 3) [188] and also projects to structures known to be involved in behavioural expression. Therefore, the Acb has been suggested to represent a 'limbic–motor interface' [190]. On histochemical and anatomical grounds, the nucleus accumbens may be divided into core (AcbC) and shell (AcbSh) compartments [162,191]. The pattern of innervation of these structures differs: the AcbC more closely

resembles the dorsal striatum, projecting predominantly to the ventral pallidum, while the AcbSh also projects to subcortical structures, such as the lateral hypothalamus and PAG, involved in the control of unlearned behaviours [163,192,193]. The DA innervation of the Acb has been extensively investigated, as it appears to play a critical role in the rewarding or motivational effect of natural reinforcers and drugs of abuse, and contributes thereby to addiction (reviewed in Refs. [54,194]). Here, we will consider its contribution to the psychological processes that motivate action, outlined earlier, and the manner in which it may be influenced by the amygdala.

4.1. The nucleus accumbens is not required for goal-directed instrumental behaviour

The available evidence suggests that the Acb is not required for goal-directed action. Balleine and Killcross [195] studied rats with excitotoxic lesions of the Acb performing a lever-pressing task. They established that these rats remained sensitive to a change in the instrumental contingency (from response-contingent to non-contingent reinforcer delivery [196]); in addition, Balleine and Killcross [195] showed that Acb-lesioned rats were sensitive to a change in the value of the instrumental outcome. By the criteria of Dickinson and Balleine [30], these rats remained capable of goal-directed action. Similarly, DA receptor antagonists do not affect the representation of reinforcer value that governs such goal-directed actions (the instrumental incentive value [70]). Insofar as the issue has been addressed experimentally, S–R habits (which probably depend on the dorsal striatum [170]) persist following Acb lesions or DA depletion [197,198], although these studies did not use outcome devaluation tests to demonstrate that behaviour was habitual.

At first sight, these results are inconsistent with studies showing that manipulations of Acb affect responding for food. For example, Kelley et al. [199] demonstrated that NMDA receptor blockade of the nucleus accumbens core (AcbC) impaired the acquisition of a lever-press response for food, though not its subsequent performance on a variable-ratio-2 schedule. Similarly, Salamone and colleagues have shown that DA depletion of the Acb reduces the ability of rats to perform instrumental responses when the work requirement is high [200]. However, both these results may be accounted for by the loss of a motivational process. For example, as NMDA receptor blockade impaired approach to the alcove where food was delivered in the study of Kelley et al. [199], it may be that subjects were not exposed to the reinforcer as often, or as soon after the instrumental response, as in control subjects. Even small response–reinforcer delays have a profoundly disruptive effect on instrumental learning [201]. In support of this motivational deficit hypothesis, Balleine and Killcross [195] themselves found that Acb-lesioned rats responded at a lower asymptotic level than controls.

Thus, when simple reinforcement schedules are used, there are many potential influences on performance. One such influence is the impact of Pavlovian CSs in the environment, and, as suggested by Balleine and Killcross [195], the Acb appears critical for the impact of these stimuli. We shall consider the involvement of the nucleus accumbens (and its regulation by the amygdala) in the processing of such stimuli, and consider its contribution to complex naturalistic and schedule-controlled behaviour.

4.2. The Acb mediates the motivational impact of Pavlovian conditioned stimuli

Pavlovian mechanisms are routinely involved when motivated animals procure goals. When a CS has been associated with an appetitive outcome, such as food, the CS will subsequently affect behaviour in several ways. In particular, it may elicit the CR of locomotor approach to the CS, a phenomenon termed autoshaping [155]. In addition, animals will subsequently work for the CS, a situation in which the CS acts as a conditioned reinforcer [27]. Finally, presentation of the CS can enhance ongoing instrumental responding [63,64], termed PIT. These effects are not merely peculiarities of learning-theory experiments, but are part of the normal interaction between an animal and its environment. Autoshaping, in which appetitive CSs attract attention and elicit approach [202,203], often has the beneficial function of drawing an animal closer to sources of natural rewards. It may also play a detrimental role in attracting humans towards artificial reinforcers such as drugs of abuse, maintaining addiction and inducing relapse [204–206]. CRf is a significant mechanism that enables animals to obtain long-term goals (recently reviewed in Ref. [76]). Similarly, PIT may be important in addiction (with potential roles in acquisition, maintenance, and cue-induced relapse [71–73]) as it represents a mechanism by which uncontrolled (non-contingent) stimuli can radically affect goal-directed responding. All three phenomena—autoshaping, CRf, and PIT—involve the AcbC.

4.2.1. Conditioned locomotor approach requires the nucleus accumbens core

Excitotoxic lesions of the AcbC, but not the AcbSh, impair the acquisition of an autoshaped appetitive approach response in rats [159]. Furthermore, AcbC lesions impair the performance of the CR in rats lesioned after the response was trained [207], just as they impair temporally discriminated Pavlovian approach to a single CS predictive of food [208]. Similarly, 6-OHDA-induced DA depletion of the Acb impaired both the acquisition [161] and performance [207] of autoshaping.

Autoshaping is not the only form of Pavlovian conditioning in which the Acb appears to give behavioural expression to associative information arising from limbic cortical afferents. At least three other tasks have been shown to operate similarly. The first is the expression of a conditioned place

preference; this depends on the BLA, but also on the Acb, and a lesion disconnecting the two structures abolishes behavioural expression [209]. The second is second-order conditioned approach: Setlow et al. [210] recently demonstrated that BLA–Acb disconnection impairs the acquisition of second-order conditioned approach behaviour, but not second-order conditioned orienting, or first-order conditioned approach—consistent with the known involvement of the BLA in second-order conditioning [107], and the Acb in conditioned approach [159,207,208]. The third is responding for CRf, discussed later. Briefly, lesions of the BLA impair responding for CRf [118]; injection of amphetamine into the Acb dramatically enhances responding for CRf [118,211], and the specificity of this enhancement depends on the integrity of the BLA—again suggesting expression of amygdala-dependent information via the Acb, and in this case revealing the additional phenomenon of modulation by the mesolimbic DA system.

4.2.2. Responding for conditioned reinforcement does not require the Acb, but is affected by accumbens manipulations

Whilst Pavlovian approach (autoshaping and conditioned magazine approach) is abolished in animals with lesions of the AcbC [159,208], the ability to use Pavlovian stimulus–outcome knowledge to guide instrumental behaviour is not, since neither the AcbC, the AcbSh, nor the DA innervation of the Acb is required for rats to acquire a new response with CRf [208,212]. Taken together, these results suggest that the Acb is involved in the expression of certain Pavlovian influences on behaviour, but is not itself a site of Pavlovian association. As discussed earlier, it is also likely that CRf does not depend entirely on Pavlovian processes. Clearly, Pavlovian conditioning is the mechanism by which a stimulus is established as a conditioned reinforcer, and this does not require the Acb. However, the *expression* of this learning might be through several mechanisms; in particular, the conditioned reinforcer may become a true declarative instrumental 'goal', responding for which does not require the Acb either [195]. The basic phenomenon of CRf (the ability to respond preferentially on a lever delivering an appetitive CS), which requires the BLA [118,119], may depend instead on direct interactions between the BLA and the OFC [145,213,214].

However, following the suggestion by Hill [215] that an important mechanism of action of psychostimulant drugs was to enhance the effects of conditioned or secondary reinforcers, amphetamine was shown to potentiate responding for CRf when injected directly into the Acb [211]. In the prototypical task, rats are first trained to associate a CS with the delivery of primary reinforcement. In a subsequent extinction test, they are presented with two levers; responding on the CRf lever results in delivery of the CS, while responding on another (non-conditioned reinforcement, NCRf) lever has no consequence. Intra-accumbens DA agonists greatly enhance responding for the conditioned reinforcer, an effect that is anatomically, behaviourally and pharmacologically specific [211,212,216]. Subsequent studies have demonstrated that the ability of amphetamine to potentiate responding for CRf depends on the integrity of the AcbSh [208], the DA innervation of the accumbens [212,216,217], and the CeA [147], once again raising the possibility that the CeA normally plays a part in controlling Acb DA during appetitive Pavlovian tasks.

Thus, it appears that information about the conditioned value of a CS depends upon the BLA and is conveyed to the Acb (though not necessarily directly or exclusively), where its effects can be potentiated or 'gain-amplified' by DA [194]. The BLA projects strongly to the Acb (both core and shell [163,218]), and while shell lesions abolish the effects of intra-Acb amphetamine, lesions of the core alter the normal response to intra-Acb amphetamine, such that amphetamine increases responding on both levers—a loss of response selectivity [219].

It remains a mystery as to precisely how the core and shell subdivisions of the Acb interact in this, or indeed any, task. Apparently, information about a conditioned reinforcer arrives at the Acb directly or indirectly from the BLA, but while the ability of amphetamine to amplify the effects of this information depends upon the DAergic innervation of the Acb and the integrity of the shell, the response selectivity of this amplification depends upon the core. Perhaps the enhancement of responding induced by intra-shell amphetamine is directed by the core towards the correct response. Though the core and shell may have direct interconnections (H.J. Groenewegen et al., unpublished observations), the shell may modify the information passing through the core via indirect routes: notably, Haber et al. [189] have shown that the shell projects not only to regions of the VTA that innervate the shell itself, but also to VTA regions that project to the core; thus, the shell may exert control over DA function in the core. Alternatively, it may be that intra-Acb amphetamine's effects on the vigour and direction of behaviour (dependent upon the AcbSh and AcbC, respectively) are not integrated within the Acb, but are integrated at downstream sites (a possible candidate being the ventral pallidum [220]).

4.2.3. Pavlovian–instrumental transfer depends upon the AcbC

CRf is a phenomenon by which a Pavlovian CS is delivered contingent upon responding. This process may involve, but not depend critically upon, the Acb. However, the accumbens is also critical for the behavioural impact of *non-contingent* Pavlovian conditioned stimuli. Non-contingent presentation of an appetitive CS elevates AcbC DA [221,222]. The functional relevance of this has been demonstrated clearly by PIT experiments. If an animal is trained to press a lever for food and subsequently tested in extinction, presentation of a Pavlovian CS that predicts the same food increases the rate of lever-pressing [63,64]. Lesions of the AcbC [144] abolish PIT [223], as does systemic treatment with DA receptor antagonists [70,224]. A recent study also

demonstrated that PIT can be enhanced by intra-accumbens amphetamine in the same way that CRf is. Wyvell and Berridge [225] trained rats to respond on a lever for food, and also paired a CS with that food. In a subsequent extinction test, they found that intra-Acb amphetamine (targeted at the AcbSh) increased the ability of the CS to potentiate responding. Finally, PIT is also impaired by CeA lesions [142,144], leading to the speculation that the ability of an appetitive Pavlovian CS to potentiate instrumental behaviour depends on the mesolimbic DA system innervating the Acb, presumably under the control of the CeA [99,144,170].

4.2.4. The relationship between PIT and conditioned reinforcement: application to drug addiction

How closely are the phenomena of PIT and CRf related? PIT is clearly not analogous to CRf itself. As discussed earlier, CRf depends on psychological processes that involve but transcend Pavlovian conditioning—although stimuli are established as conditioned reinforcers by Pavlovian conditioning, they probably also acquire instrumental incentive value [75,226]. However, PIT and CRf are not dissimilar. Importantly, there is potential for conditioned reinforcers to influence behaviour via PIT. When an animal responds and earns a conditioned reinforcer, the CRf obviously cannot affect the response that produced it, but it could affect *subsequent* responding in the same manner that non-contingent CSs do (i.e. via PIT).

PIT and CRf have been dissociated neurally: for example, BLA lesions impair CRf but not PIT [110,118,119,144], while AcbC lesions impair PIT but not CRf [144,208]. However, there is a good match between the neural bases of PIT and the artificial phenomenon of *amphetamine potentiation* of CRf (see above). Both involve the DAergic innervation of the Acb. The potentiation of CRf by amphetamine depends upon Acb DA [212,216,217], while non-contingent presentation of an appetitive CS elevates Acb DA (specifically in the AcbC [221,222]) and PIT may also depend upon the Acb DA innervation, as it is abolished by systemic DA antagonists [70] and enhanced by intra-Acb amphetamine [225]. Both amphetamine potentiation of CRf [147] and PIT [144] depend on the CeA, and we hypothesize that this is because the CeA influences Acb DA via the VTA (a suggestion that has neuroanatomical support [86,166–169]). Furthermore, lesions of the BLA remove the source of information to the Acb regarding CRf that determines the specificity of amphetamine potentiation of CRf [118,119]; similarly, BLA lesions impair the response selectivity of PIT [143] but do not abolish the basic PIT effect [142–144]. Core lesions can sometimes abolish PIT [144], and they also abolish amphetamine potentiation of CRf—in that the ability of amphetamine to potentiate responding for a CRf in a selective manner is lost, though amphetamine still potentiates responding in a non-selective manner in AcbC-lesioned animals [208]. Shell lesions abolish amphetamine potentiation of CRf [208] and can abolish PIT [196,227], though not in all tasks [142,144].

Thus, though ambiguities remain, it may be reasonable to suppose that potentiation of CRf by amphetamine reflects artificial activation of the system by which *non-contingent* Pavlovian CSs normally increase the probability of instrumental responses (PIT). This system appears to play a minor role in responding for CRf under normal situations (thus, responding for CRf survives AcbC lesions, AcbSh lesions, and DA depletion of the Acb [208,212]), possibly reflecting the fact that typical CRf experiments use brief conditioned reinforcers that cannot significantly potentiate responding via PIT. However, the efficacy of this system may be dramatically enhanced following repeated exposure to drugs of abuse such as psychostimulants [228], which activate DA systems more consistently than food reinforcers do [229]. Addictive drugs may be unique among reinforcers at producing sensitization, the phenomenon by which repeated drug administration leads to an enhanced response to the drug (for reviews, see Refs. [205,230,231]). Psychostimulant sensitization induces hypersensitivity to DAergic stimulation of the Acb [232]. It enhances Pavlovian conditioned approach [233], which depends on the CeA, the AcbC, and the DA innervation of the Acb [105,159], and it enhances the potentiation of CRf by intra-Acb amphetamine [228], which also depends on this circuit [147,208,212,216,217]. An obvious prediction is that PIT would also sensitize; this has recently been confirmed [373]. However, it is clear that at least some of the Pavlovian motivational processes provided by the Acb and its DA innervation, termed *incentive salience* or 'wanting' by Robinson and Berridge [54,230], do sensitize (as suggested in Ref. [230]); such 'incentive sensitization' may be an important contributor to addiction.

4.3. The AcbC promotes responding for delayed rewards

Finally, it has recently been shown that the integrity of the Acb is also critical for animals to tolerate delays to reward. In a task in which rats were offered the choice of an immediate, small reward or a larger, delayed reward, selective lesions of the AcbC severely impaired rats' ability to choose the delayed reward; that is, AcbC-lesioned rats made impulsive choices [234]. The possibility that the AcbC is required to maintain the value of a reinforcer over a delay may provide a novel insight into Acb function, as it is not clear that deficits in the expression of Pavlovian conditioning can account for this result. Neuronal activity in the primate ventral striatum is related to the expectation of reward across a delay; such activity is a candidate representation of the goals of behaviour [235]. Striatal neurons also respond to past events, maintaining a form of memory that might assist the association of past acts with reinforcement [235]. These findings are the basis for computational models of striatal function [236] and indicate the nature of the information that the AcbC may use to promote actions

leading to delayed rewards. Additionally, the results of Cardinal et al. [234] demonstrate a role for the Acb in action selection even when those actions do not differ in response effort or cost. Thus, reduced preference for delayed reinforcement may also explain the observations that Acb DA depletion prevents rats working hard for a preferred food [237] and impairs responding on high-effort schedules [200], as such schedules also impose delays to reinforcement. It is not presently known which afferents convey specific information about the value of delayed reinforcers to the AcbC, but as lesions of the anterior cingulate cortex (ACC) or medial prefrontal cortex (mPFC) had no effect on impulsive choice [234], obvious candidates are the BLA and OFC, both implicated in the assessment of reward value and probability [100,238]. Indeed, Mobini et al. [374] have recently shown that lesions of the OFC induce impulsive choice in a manner similar to AcbC lesions.

4.4. The nucleus accumbens shell mediates the motivational impact of unconditioned stimuli

There is less behavioural evidence relating the AcbSh to specific learning processes. For example, lesions of the AcbSh leave aversive Pavlovian conditioning to both discrete and contextual cues intact [219], do not impair appetitive Pavlovian approach behaviour [159,208], and do not prevent rats responding for CRf [208]. However, extracellular DA release, particularly within the AcbSh, has been shown to be sensitive to primary reinforcers. In particular, DA increases in the AcbSh have been reported in response to unconditioned stimuli such as food [222] and, not surprisingly, cocaine [221]. In fact, unconditioned *aversive* stimuli also increase DA release in the Acb [239], specifically the AcbSh [240]. However, *conditioned* stimuli do not elevate AcbSh DA, elevating DA in the AcbC instead [221,222,241].

In turn, the AcbSh influences a number of unlearned behaviours. Kelley and colleagues have demonstrated elegantly that the AcbSh appears to provide an influence on feeding through its interactions with the lateral hypothalamus [242]. For example, selective intra-AcbSh infusions of the AMPA receptor antagonist DNQX or the GABA(A) receptor agonist muscimol stimulate feeding [243–245]. This effect resembles that seen following electrical stimulation of the lateral hypothalamus; indeed, the feeding induced by DNQX infusion into the shell can be blocked by concurrent inactivation of the lateral hypothalamus [246]. It has been argued that the AcbSh provides a high-level control system able to switch between basic behavioural patterns based on primary motivational states; for example, to override feeding behaviour if a predator approaches [242]. Like the AcbC, the AcbSh also influences locomotor behaviour: DAergic stimulation of the AcbSh induces locomotion [247], while the locomotor stimulant effects of amphetamine depend on the AcbSh [208]. Thus, it is tempting to speculate that whilst the AcbC mediates a conditioned influence on behaviour, the AcbSh may provide a qualitatively similar influence, but responding to unconditioned stimuli.

4.5. Implications for the involvement of the Acb in naturalistic and schedule-controlled behaviour

The interpretation that the Acb (specifically, the AcbC) contributes Pavlovian conditioned motivation to behaviour is compatible with the view that it mediates aspects of preparatory behaviour, temporally distant from the goal of behaviour (as opposed to consummatory behaviour, temporally close to the goal). As an example of such a distinction, lever-pressing by male rats for access to a female has been doubly dissociated from unconditioned sexual behaviour [248,249]. In different settings, this distinction has been phrased in various ways—preparatory versus consummatory [194,250], seeking versus taking [100,251], and sign tracking versus goal tracking [202]. Manipulations of the Acb, including 6-OHDA lesions and systemic injections of DA receptor antagonists, have been shown to reduce the preparatory aspects (including rate of responding) of behaviour directed towards both food and (in male rats) a sexually receptive female, whilst leaving consummatory behaviour unaffected [250,252–255]. Schedule-induced polydipsia (SIP), a phenomenon whereby excessive drinking is produced by the intermittent presentation of small amounts of food, is a preparatory behaviour attributable to motivational excitement and is dissociable from thirst-induced drinking; it is also disrupted selectively by 6-OHDA lesions of the Acb [256,257]. In almost all paradigms studied, manipulations of limbic corticostriatal circuitry affect preparatory but not consummatory behaviour [194]. The functional importance of such behaviour has been demonstrated by Whishaw and Kornelsen [258]. Rats normally carry food to a refuge to eat it, and when sated, carry the remaining food to hoard; rats with excitotoxic or 6-OHDA lesions of the Acb were selectively impaired in this preparatory behaviour, failing to carry food to hoard it, while still carrying-to-eat and eating normally.

These motivational processes undoubtedly contribute to performance under different schedules of reinforcement. For example, Salamone and colleagues have demonstrated that 6-OHDA-induced DA depletion of the Acb causes rats to forgo the opportunity to press a lever for a preferred food, instead consuming more of a less-preferred but freely available food [259,260]; such DA depletion impairs responding on high-rate but not on low-rate schedules [200,261–263]. These impairments cannot be attributed entirely to motor deficits [264]. These results allow two explanations within the framework we have outlined. Firstly, as discussed earlier, they may reflect impairments in the efficacy of delayed reward. Secondly, these results are compatible with the loss of a DAergic motivational influence that contributes to normal performance; indeed, Acb DA

depletion also impairs irrelevant 'displacement' behaviour occurring when food is delivered on a fixed-time schedule [257]. Such behaviour cannot easily be described as carrying a response cost, but it may reflect a potentiation of irrelevant available behaviours by a motivational effect of the food [257].

Finally, while it is at present difficult to establish the contribution of well-defined Pavlovian and instrumental processes (such as conditioned approach) to complex spatial behaviour as assessed in typical spatial learning tasks, it should be noted that the DA-dependent processes within the Acb contributes to the consolidation of rats' memory for water maze tasks [265–267], consistent with hypothesized roles for DA in learning [170]. Thus, it appears that spatial learning, like instrumental learning, is modulated by the Acb, but does not require it [268].

4.6. Summary

The nucleus accumbens has a role in modulating unconditioned behaviours such as feeding and locomotion, and learned behaviour (including instrumental responding). It is a key site mediating the ability of Pavlovian CSs to invigorate and direct behaviour, being critical for autoshaping (the influence of Pavlovian CSs on locomotion), the effect of psychostimulant-amplified conditioned reinforcers on instrumental responding, and PIT. This motivational influence of Pavlovian CSs has been termed incentive salience [54,230], or 'Pavlovian incentive value' [70], to distinguish it from the instrumental incentive value of Dickinson and colleagues [29,30]. Additionally, the Acb appears to support animals' ability to work for delayed rewards; one possible explanation is that the Acb provides motivation to choose a delayed reward that normally offsets the effects of the delay.

5. The prefrontal cortex and its interactions with the amygdala and ventral striatum

In the rat, the PFC is a heterogeneous region of the brain that includes the prelimbic, anterior cingulate, agranular insular and orbitofrontal areas [164,269]. Each of these regions makes a distinct contribution to emotional or motivational influences on behaviour. Though the contribution of the PFC to conditioning is likely complex, and certainly not understood in detail, recent studies have shed some light on the processes that might be subserved by prefrontal cortical subregions, and on their interaction with the amygdala and Acb (Fig. 3). This final section will review studies that have examined the contribution of the PFC to simple conditioning tasks, and will of necessity omit a great deal of research into complex functions of the PFC (such as working memory, attention and 'executive' control [270]). In this section, we will emphasize studies of the rat. However, there is also a compelling literature regarding the contribution of the anterior cingulate and orbitofrontal cortices to emotion in humans. Despite the fact that the PFC has undergone considerable phylogenetic expansion in primates, leading to difficulties in establishing correspondence between primate and rodent PFC subregions, both anatomical and functional comparisons are possible [271,272]. Comparisons will therefore be drawn between functional studies of the ACC and OFC in primates and rodents.

5.1. Prelimbic cortex: instrumental contingency detection and extinction

In the rat, the contribution of the prelimbic cortex (part of the medial prefrontal cortex, mPFC) to motivated behaviour appears to involve the detection of instrumental (A–O) contingencies. It is important to note that to demonstrate that a structure is necessary for detection of A–O contingencies requires more than showing that an animal cannot acquire instrumental responding in its absence. Indeed, were one to prevent an animal from perceiving contingencies, there is every reason to think that instrumental performance *would* be acquired, via a habit system. Explicit tests of contingency perception are thus required. For example, rats may be trained to perform two actions concurrently for two different food rewards; in addition, one of those reinforcers may be delivered non-contingently with respect to the subjects' behaviour. The degree of A–O contingency for this reinforcer, $P(\text{outcome}|\text{action}) - P(\text{outcome}|\text{no action})$, is thus selectively degraded. In one of the few lesion studies to date to use this technique, Balleine and Dickinson [273] found that although lesions of prelimbic cortex did not prevent rats acquiring instrumental performance, or, in separate tests, from discriminating between the two actions and the two reinforcers, they rendered the rats insensitive to this contingency manipulation, suggesting that such rats might truly be 'creatures of habit'.

Goal-directed action requires that instrumental contingencies interact with the incentive value of goals, and as described earlier, the BLA may be involved in the neural representation of incentive value. Interestingly, the connection between the BLA and the mPFC has recently been shown to be involved in the ability of rats to modulate instrumental choice behaviour in response to conditioned punishment [274]; thus, the anatomical connection between the BLA and the mPFC [85] might conceivably represent a functional link between incentive value and instrumental contingencies.

Additionally, electrolytic lesions of the the ventral mPFC, i.e. prelimbic/infralimbic cortex (but not dorsal mPFC or ventrolateral, agranular insular cortex) interfere with the extinction of Pavlovian conditioned freezing to a discrete CS in the rat [275–277]. Similarly, the prelimbic cortex in the mouse interacts with the amygdala and may function to suppress inappropriate conditioned freezing [278]. As extinction does not simply represent 'unlearning' but may involve the learning of new, inhibitory ('CS → not-US') associations [27], these findings may be related to the long-standing view that the PFC mediates behavioural

inhibition [279–281], with different specific aspects of inhibition being mediated by different regions within the PFC [282,283]. Reconciling these perspectives on prelimbic cortex function will require both experimental and theoretical developments.

5.2. Insular cortex: memory for specific sensory aspects of food, used to retrieve value information

Balleine and Dickinson [273,284] also investigated the role of the insular cortex, the primary gustatory cortex in the rat [285], in incentive learning for food rewards. Lesioned rats performed normally on the instrumental contingency test just described. In addition, a specific satiety test was conducted, in which the rats were fed one of the two foods to satiety, thus giving them the opportunity to learn that this food had reduced value in the sated state (see *Incentive learning*, earlier). The rats only ever experienced the other food whilst hungry. Finally, the rats' instrumental performance was tested in extinction while sated. While sham-operated control rats responded less for the reward that had been devalued, insula-lesioned rats failed to make this discrimination. However, in a further test in which the reinforcers were actually delivered, they discriminated immediately. This suggests that the insula is not a critical structure for determining instrumental incentive value, but is critical for storing or retrieving the memory of the incentive value in the absence of the reward. Balleine and Dickinson [284] suggest that insula-lesioned rats cannot recall this incentive value because they cannot remember the *specific sensory* properties (tastes) of the instrumental outcomes. Incentive value can be retrieved via tastes [286,287], and this hypothesis accords with the known gustatory functions of insular cortex [288,289], although it implies some degree of dissociation between primary perception of taste (normal in insula-lesioned rats [290]) and taste memory.

The insular cortex may have a similar role in Pavlovian conditioning: mnemonic retrieval of specific sensory aspects of the food US may depend on gustatory neocortex [115]. Kiefer and Orr [288] have shown that rats with gustatory neocortex lesions reduce their consumption of a flavour paired with LiCl, and show normal unconditioned orofacial rejection responses, but do not show conditioned orofacial responses. Conditioned orofacial responses [50,291] may depend on the retrieval of specific sensory aspects of the US [292,293]. Thus, Holland [115] has suggested that insula-lesioned rats have access to the conditioned motivational value of the food (hence the rats drink less following conditioning), and perceive tastes normally, but cannot retrieve the taste of the food using a CS.

5.3. Orbitofrontal cortex and representations of reinforcer value

The OFC has been widely suggested to guide behaviour based on the anticipated value of different actions [294,295]; it is extensively and reciprocally connected to the BLA (reviewed in Ref. [271]). Humans with OFC damage are impaired on a number of tests of emotional reactivity to stimuli, and make poor decisions as a result [296]; in several respects, they resemble amygdala-lesioned subjects [297]. For example, in the laboratory 'gambling task' of Damasio and colleagues (reviewed in Ref. [296]), subjects choose between decks of cards; some decks pay out small rewards steadily, with the occasional small loss, for a net gain, while other decks pay out much larger rewards but the occasional losses are catastrophic. Normal subjects learn to prefer the safe decks, and develop an autonomic response (including a skin conductance response, SCR) that precedes their choice and is especially pronounced when they are about to choose a 'risky' deck. OFC-lesioned patients do not develop anticipatory SCRs and consistently perform poorly on the task. Damasio et al. have suggested that these autonomic responses represent 'somatic markers' [295], a rapidly retrieved 'utility signal' that normally acts to speed up and improve decision-making by 'prebiasing' other, computationally intensive cognitive systems, preventing them from considering particularly bad courses of action.

Such decision-making may represent instrumental choice behaviour based on the incentive value of the alternative outcomes. The OFC is a particularly strong candidate for a representation of incentive value, as its neurons respond rapidly to changes in the reward value of specific foods. For example, neurons in primate OFC respond to reward but discriminate between different rewards in doing so [235,298]. When a monkey is fed to satiety with a particular food, the OFC responses to its flavour or odour decline, while the responses to other foods are unaffected [299], paralleling the behavioural change induced by sensory-specific satiety. Similarly, OFC lesions impair monkeys' ability to alter behaviour in response to changes in the emotional significance of stimuli [282,283]. Like the amygdala, the OFC is well placed to process specific value information, as it receives projections from polymodal sensory cortex [271] in addition to motivational state information from the hypothalamus.

The relationship between the OFC and the amygdala is at present unclear; however, the two certainly subserve related functions. Although Rolls has suggested that primate OFC acts as a highly flexible system that *takes over* functions of the more primitive amygdala [299], Schoenbaum et al. [300] found evidence that, in the rat, the BLA rapidly learns to respond to CSs according to the motivational value of the US, while changes in the electrophysiological response of OFC cells follow later and are more clearly related to choice behaviour. OFC lesions prevent rats from adjusting their conditioned responding appropriately following US devaluation [213], just as BLA lesions do [107]. Humans with amygdala lesions perform badly on the gambling task of Damasio et al. [297], choosing poorly and failing to develop anticipatory SCRs just as OFC-lesioned patients do;

however, amygdala-lesioned patients appeared to have the more fundamental deficit, as Pavlovian SCR conditioning was impaired in amygdala-but not OFC-lesioned patients [297]. Again, this suggests that the OFC builds upon more basic conditioning functions provided by the amygdala. Recently, direct evidence for a functional connection between the BLA and OFC has been provided by Baxter et al. [145], who showed that disconnecting these two structures impaired the ability of rhesus monkeys to adjust their choice behaviour in response to reinforcer devaluation. These data are all consistent with the notion that the OFC influences instrumental choice behaviour and interacts with value systems in the amygdala to do so, but more investigation is required to establish the nature of this interaction.

5.4. Anterior cingulate cortex: mood, error detection, and stimulus specificity of conditioned responses

The ACC is part of the midline PFC that has been strongly implicated in emotional processing. Although a rough equivalence may be drawn across the ACC of rodents, monkeys and humans [271,301], the focus of research on the primate ACC has so far differed from that on the rat; both concern motivated behaviour, however, and so they will be reviewed and compared.

It must be borne in mind that although many studies in primates concerned with the ACC have used non-excitotoxic lesion techniques [302], such lesions bring particular problems. Any lesion that destroys the cingulum bundle will disconnect large portions of cortex, as this bundle contains not only all afferent and efferent connections of the cingulate cortex, but also fibres that pass to and from the rest of the prefrontal (including orbitofrontal) cortex—notably the reciprocal connections between the PFC and the medial temporal lobe [303]. Thus such studies must be interpreted with caution. Additionally, many studies have concentrated on unconditioned (unlearned) behaviour. It is clear that the primate ACC, at least, is involved in a wide range of motivationally oriented unconditioned behaviour [302]. In the present article, however, we will concentrate on aspects of ACC function regarding emotions and emotional learning.

5.4.1. Primate ACC function

Isolated destruction of the human ACC is rare [302], so lesion studies of humans have mostly been of patients with frontal lobe tumours. ACC lesions have produced a wide variety of symptoms, including apathy, inattention, autonomic dysregulation, emotional instability, and akinetic mutism [302,304]. However, such studies are often compromised by a lack of anatomical specificity: tumours and epileptic foci do not respect anatomical boundaries, and if these tumours involve the ACC, their resection inevitably compromises the cingulum bundle, and thus OFC function. Indeed, many of the patients studied by Damasio and colleagues have had ACC damage in addition to orbitofrontal lesions [296]. However, much information regarding human ACC function has been obtained using techniques that aim to observe differences in ACC activity correlated with task performance or mental state (albeit without inferring causality). These studies have implicated the primate ACC in four interrelated functions.

Mood. The anterior, ventral ACC (Brodmann's areas 24a/b and 25), part of the 'affective' subdivision of the ACC [302], is now strongly implicated in the pathology of depression in humans [305], as well as in the control of normal mood. Drevets et al. [306] observed that this area of the ACC ('subgenual PFC' or subgenual area 24 [307]) showed decreased blood flow in unmedicated familial bipolar and unipolar depressives using positron emission tomography (PET), though this was in part due to a reduced grey matter volume as assessed by magnetic resonance imaging (MRI); if this is corrected for, blood flow per unit volume was increased [308,309]. Mayberg et al. [308,310,311] have demonstrated similar abnormalities; metabolic activity in rostral ACC (rostral area 24a/b) is also unique in differentiating those depressed patients who eventually respond to pharmacological antidepressant therapy from those that do not [312]. Areas 24a/b and 25 are also part of a cortical network whose metabolic activity alters in normal sadness [313]. Mayberg et al. [313,314], reviewing these data, have suggested that hyperactivity of subgenual area 24/area 25 is a primary factor in sadness and depression, causing reciprocal suppression of metabolism in adjacent ACC and dorsolateral PFC, which may explain the efficacy of surgical destruction of the subgenual cingulate as a therapy for refractory depression.

Emotional significance of stimuli. Imaging studies have also shown that the human ACC responds to emotionally significant stimuli. It is reliably activated by cocaine-associated cues in cocaine users, more so than by neutral stimuli in the same individuals, or by cocaine-associated cues in non-users [315–317]; such activation may be associated with cocaine craving [315,317–319]. While fewer studies have examined the effects of natural reinforcers, it appears that the ACC is similarly activated by emotionally significant non-drug stimuli in normal humans (sexual images [316]).

Attention and action. In humans, PET studies have provided evidence that the ACC is involved in executive attention. In attentional target detection tasks, blood flow increases with the number of targets to be detected, while flow to the anterior cingulate gyrus is reduced below baseline during the maintenance of vigilance (reviewed in Ref. [185]). These PET studies have also suggested a role for the ACC in 'willed' tasks, perhaps with a motivational role [320]; along with dorsolateral PFC, blood flow to ACC is significantly increased in tasks requiring a voluntary choice of action, compared to routine, well-rehearsed actions [321].

Detecting errors or response conflict. While studying choice reaction times (RTs) in humans, it was observed that a negative EEG potential was evoked when subjects made an error [322–324]. This potential was named the

error-related negativity (ERN; for reviews, see Refs. [325–327]). The ERN is hypothesized to reflect part of a process in the brain that monitors ongoing actions, compares them with intended actions, detects any mismatch, flags the presence of an error if mismatch exists, and takes action to correct ongoing or future performance [323,328,329]. In support of early speculations [323], recent research points to the ACC as the likely source of the ERN [304,330,331]—indeed, the ERN may have first been noticed by researchers recording directly from the ACC (area 24) in macaque monkeys [332]. The ACC has therefore been likened to a supervisory attentional system [333,334]. Given the importance of error signals in many models of learning (famously, that of Ref. [176]), there has been considerable interest in relating the ERN to learning [335,336], although the data summarized here suggest that the ACC's functions are more to do with response errors than errors of reward prediction [335].

Comparable results have been obtained using functional imaging studies. Several such studies have used the Stroop task [337]: in a typical version of this task, the subject must report the colour of a series of words, while ignoring the word itself. In the critical, 'incongruent' condition each word is the name of a colour that differs from the colour in which the word is printed; performance is poorest in this condition. The Stroop task elicits an ERN from the ACC [338] and strongly increases metabolic activity within the ACC [339]; indeed, versions of the task using neutral stimuli activate a different subregion of the ACC to versions that use emotionally charged stimuli [304,340–342]. However, the emphasis of functional imaging studies to date has been on the process of action selection [343–345], or the detection of response competition or conflict rather than overt errors [238,342,346,347].

5.4.2. Rodent ACC function

The rodent ACC has been strongly implicated in appetitive and aversive stimulus-reinforcer learning. It receives nociceptive information and coordinates autonomic responses [301,348,349]; early studies found that aspirative ACC lesions attenuated classically conditioned bradycardia in the rabbit [350]. The rabbit ACC is also involved in active avoidance behaviour, a task combining aspects of Pavlovian and instrumental conditioning. When rabbits must learn to step in response to a tone CS+ in order to avoid a shock, while ignoring a different tone (CS−), Gabriel et al. have shown electrophysiologically that discriminated neuronal activity (discharge to the CS+ but not the CS−) develops early in avoidance training [351–354]. Lesions of the ACC impair acquisition of the avoidance response [355,356], attributed to the loss of associative information about the significance of a discrete CS [353].

In the rat, the ACC has been more extensively studied using appetitive tasks, which also suggest that it has a role in stimulus–reinforcer association. For example, Bussey et al. [357] found that lesions of the ACC impaired the acquisition of an eight-pair concurrent discrimination task, in which subjects must learn which stimulus in each of eight pairs of complex visual stimuli must be selected in order to obtain reward. Furthermore, ACC lesions impair the acquisition of stimulus–reward associations in autoshaping, a selective test of Pavlovian conditioning described earlier [43,159].

The ACC projects to the nucleus accumbens core (AcbC) [162,163,193,358,359]. As the ACC and AcbC are both required for autoshaping, one possibility is that they function as part of a single corticostriatal circuit, in which stimulus–outcome associations stored or retrieved by the ACC gain behavioural expression through the AcbC. This hypothesis was tested directly using a 'disconnection' procedure, in which asymmetric unilateral lesions of both the ACC and the AcbC were made in order to prevent communication between the two structures; this disconnection lesion impaired autoshaping, though single unilateral lesions of either structure did not [159]. Thus, the ACC appears to provide the critical glutamatergic projections to the AcbC for autoshaping, as lesions of posterior cingulate cortex (PCC), mPFC, ventral or dorsal subiculum or the BLA do not impair autoshaping [43,105,360].

Although the data summarized earlier strongly implicate the ACC in stimulus–reinforcer association, recent findings suggest that Pavlovian conditioning can occur in the absence of the ACC and suggest that the ACC makes a highly specific contribution to conditioning. Unexpectedly, we found that ACC-lesioned rats could learn simple conditioned approach tasks, despite being impaired at autoshaping; they could also utilize a Pavlovian CS as a conditioned reinforcer, and exhibited normal conditioned freezing and PIT. Thus, they performed normally in all tasks in which a single CS was used, but were impaired on tasks involving multiple CSs (including autoshaping and a two-stimulus approach task designed to establish the critical behavioural difference between autoshaping and the simpler, one-stimulus conditioned approach task at which they were unimpaired). It is noteworthy that multiple CSs have been used in a wide range of other tasks in which ACC lesions impair performance [43,159,355–357,361,362]. On the basis of these data from rodents, we have suggested [170,363] that the ACC 'disambiguates' similar CSs for its corticostriatal circuit on the basis of their differential association with reinforcement, preventing generalization between the CSs.

As the BLA and ACC both contribute to processes of Pavlovian conditioning, how do their functions differ? The ACC provides specific information to the Acb via glutamatergic projections, through which it influences response selection in conditioned approach tasks [159], just as the BLA appears to do for CRf [118] and perhaps for PIT [143]. In all these tasks, the glutamatergic information is in some manner 'gated' or amplified by the DAergic innervation of the Acb, probably under the control of the CeA [105,144,147,161,216]. Taking these data together, it is suggested that the contributions of the BLA and ACC differ in the following way: the BLA uses a CS to retrieve

the motivational value of its specific US, while the ACC directs responding on the basis of the specific CS, preventing generalization to similar CSs. Though these roles are different, and the contributions of the two structures have been dissociated in a number of tasks [43,118,363,364], they are not dissimilar, and it is a goal of future research to determine how and why these two interconnected structures communicate.

5.4.3. Relating rodent and primate ACC function

It would be optimistic to be able to relate the entire literature on human ACC function to studies of rats, mice, rabbits, and monkeys. In particular, there is little evidence to address the question of whether the rodent ACC responds to errors or response–conflict situations (though the macaque ACC does [332]), and there are few anatomically well-specified human lesion studies investigating the behavioural role of the ACC. However, common themes can be drawn. The rostral division of the human ACC responds to stimuli of affective significance [340], as does the rabbit ACC [351–354]. The rabbit ACC uses this information to contribute to the selection of actions in instrumental avoidance tasks, a function similar to that attributed to the human ACC, and both the human and the rodent ACC control a wide variety of skeletomotor and autonomic response systems [43,302,343–345,362]. The rat ACC contributes to the control of behaviour when faced with two or more similar stimuli predicting different outcomes [43,159,355,357,362,363]; analogies may be drawn with human 'response conflict' accounts. The human ACC is suggested to be activated by novelty or errors [322,323,330,331,365] and thus to be involved in learning [335,336]; it is activated early in the acquisition of new tasks [366,367]. Similarly, the contribution of rodent ACC is most marked early in training, when most learning might be expected to occur [159,353,356,368–370]; the monkey ACC ERN is present only during learning, when errors are still being made [332], and the mouse ACC appears to contribute to performance when response–outcome contingencies are changing rapidly [361]. It is to be hoped that future studies will begin to bridge these two literatures.

5.5. Summary

The PFC makes many contributions to motivated behaviour; its functions are starting to be related to basic processes of Pavlovian and instrumental conditioning. Analysis of the basic processes performed by the PFC will likely provide a foundation from which to understand its contribution to complex functions such as 'executive control'. Additionally, PFC subregions, particularly the OFC and ACC, make important contributions to representations of value and emotion. The prelimbic cortex, involved in working memory and attention (functions that have not been discussed here), has also been implicated in A–O contingency detection, while the rodent insular cortex has a role in mnemonic retrieval of taste information (and through it, representations of incentive value). The OFC is a strong candidate for the representations of instrumental incentive value, and interacts heavily with the amygdala. The ACC has been directly implicated in human emotional disorders; it may respond to the emotional significance of stimuli but also to errors of performance, using this information to 'disambiguate' responding and prevent responding to inappropriate stimuli. Recent interventional studies in rodents are beginning to make links to correlational studies in humans with the aim of a better understanding of the mechanisms of motivation.

6. Conclusions

Emotion, motivation and reinforcement are not unitary. Pavlovian conditioning creates multiple representations (Fig. 1), whose neural bases are dissociable and gradually becoming clear. These include CS–US(sensory) or S–S associations, dependent at least in part on the perirhinal cortex for visual stimuli and on the gustatory neocortex for food USs; CS–US(motivational) associations, suggested to depend on the BLA for both appetitive and aversive conditioning; direct CS–affect associations, which are poorly understood; and CS–response associations, whose neural basis depends on the specific response (being cerebellum-dependent in the case of discrete skeletomotor CRs, and CeA-dependent in the case of several others such as conditioned suppression and PIT). The ACC is also implicated in stimulus–reinforcement association and the attribution of emotional significance to stimuli; it may act to prevent other neural systems from generalizing between CSs erroneously, though there are many aspects of human and rodent ACC function that are not yet reconciled.

Other structures contribute to instrumental conditioning, which also creates multiple representations (Fig. 2) and which can be heavily influenced by Pavlovian conditioning procedures. At least some of the processes governing instrumental responding are based on declarative knowledge akin to symbolic processing, even in rats, and yet these complex representations are known to interact with each other and with basic motivational states to generate willed action. The prefrontal (prelimbic) cortex is critical for the perception of instrumental contingencies in rats, while gustatory neocortex also has a role in recalling the instrumental incentive values of foodstuffs. It is not yet known how either structure acquires or represents this information, or how each interacts with other representations of stimulus and reward value such as those in the amygdala and OFC (Fig. 3). It seems likely that the dorsal striatum contributes in some way to the acquisition of S–R responding [170], but this requires definitive proof. The nucleus accumbens was accurately described by Mogenson et al. [190] as a limbic–motor interface, but it may also be considered a Pavlovian–instrumental interface; in addition

to promoting the efficacy of delayed rewards, it is a critical site for the motivational and directional impact of Pavlovian CSs on instrumental responding and on locomotor approach.

Finally, this review has concentrated on the neural representations which govern animals' *performance*, rather than the learning mechanisms by which they are acquired. While learning theorists emphasize a view of animal learning based on a general-purpose, limited-capacity learning system [17], neurobiological studies have demonstrated that performance is dependent upon multiple representations. At present, there is no clear idea how these two aspects of the nervous system interact—how learning occurs across a distributed set of systems, according to similar rules, in a coherent fashion. This might either be because highly complex associative rules are embedded on a small scale (such as at the level of the neuron) in a wide variety of neural tissue, and very consistently so, or that some (as yet unknown) central, cooperative learning mechanism regulates learning in widely distributed areas of the brain. There is direct psychological evidence for the latter idea [17,371,372], and the elucidation of the neural basis of this mechanism is an exciting challenge.

Humans are plagued by disorders of emotion (such as depression, anxiety, and phobias) and motivation (such as impulsivity and addiction); it is crucial for rational therapeutic developments that the neural systems described in this article are understood. The application of well-defined psychological concepts to neuroscientific studies can only aid this understanding.

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